

Pharmacology of Blood



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This chapter deals with the following drugs:

I- Hemostatics and Coagulants: Drugs used to stop bleeding.

II- Anticoagulants:

Drugs used in prevention and treatment of thromboembolic diseases in vivo and are particularly effective in **venous thrombosis**. They are also used to prevent blood clotting in blood samples and during blood transfusion (in vitro).

III- Antiplatelets (Antithrombotics):

Drugs used to prevent platelet aggregation. They are particularly effective in prophylaxis against **arterial thrombosis** as coronary thrombosis causing acute myocardial infarction. N.B.: arterial thrombi are formed of platelet aggregation mainly and are thus known as **"white" thrombus**, whereas venous thrombi are formed of fibrin mainly which entangles RBCs and are called **"red" thrombi**. A part of venous thrombi may detach forming an embolus (floating thrombus).

IV- Fibrinolytics (Thrombolytics):

Drugs used to dissolve (lyse) already formed thrombi and emboli, mainly arterial thrombi as in acute myocardial infarction due to coronary thrombosis.

V- Antihyperlipoproteinemic Drugs (Antihyperlipidemics): Drugs used in treatment of hypercholesterolemia and / or hypertriglyceridemia.

VI- Antianemic Drugs: Drugs used to treat anemias.



I-Hemostatics and Coagulants

A-Local Hemostatics (styptics):

- 1- Physical methods:** application of pressure (compression), cold, or cautery (e.g. by diathermy).
- 2- Vasoconstrictor drugs** as adrenaline and ephedrine locally in cases of epistaxis (contraindicated in hypertension and bleeding from fingers, toes and during male circumcision).
- 3- Astringents** as tannic acid and alum, which precipitate surface proteins at sites of bleeding.
- 4- Local coagulants** to stop bleeding from minute vessels:

a-Thrombin and thromboplastin.

b-Human fibrin foam (**sponge**)
used in surgery.

c-Absorbable gelatin sponge.

d-Oxidized cellulose (**oxycel**): surgical gauze which acts mechanically but should not be left for long time as it prevents epithelization.



B-Systemic Coagulants:

1-Vitamin K:

- It is obtained from diet and is also synthesized by bacterial flora.
- It is a fat-soluble vitamin, so absorption is impaired in cases of obstructive jaundice and by liquid paraffin (lubricant purgative).
- It is reduced in the liver into an active form. Reduced vitamin K is active and is essential for activation - by carboxylation- of coagulation factors II (prothrombin), VII, IX, and X, and of anticoagulation proteins C and S. After carboxylation of these factors, reduced active vitamin K is converted into inactive vitamin K epoxide which is transformed again into active reduced vitamin K by vitamin K epoxide reductase which is inhibited by oral anticoagulants as warfarin and by large doses of salicylates (aspirin).

Vitamin K-----► reduced active vitamin K -----Carboxylation
(activation) of coagulation factors + inactive vitamin K epoxide.

Vitamin K epoxide reductase

Vitamin K epoxide -----► reduced active vit.K
(inhibited by warfarin and large doses of aspirin)

- Vitamin K is the specific antidote of oral anticoagulants.
- Vitamin K is used in treatment of bleeding due to hypoprothrombinemia which is caused by:

-Drugs: Overdose of oral anticoagulants and salicylates.

-Decreased synthesis of vitamin K by flora: Prolonged use of oral broad spectrum antibiotics especially if incompletely absorbed as

ampicillin,

cefadroxyl, and tetracycline.

-Excessive metabolism of vitamin K: Antiepileptics as phenytoin, phenobarbitone, primidone (partially converted into phenobarbitone), and carbamazepine (all are HME inducers).

-Decreased absorption of vitamin K: Liquid paraffin (decreases vitamin K absorption), obstructive jaundice, malabsorption syndrome, and by drugs as neomycin.

-Decreased utilization of vitamin K in liver: Liver diseases and neonates especially if premature.

2-Protamine sulphate:

basic and electropositive drug -chemically antagonizes heparin (which is strongly acidic and electronegatively charged) -specific antidote of heparin used to control bleeding due to overdose of heparin-given IV.



3- Antifibrinolytics: as Tranexamic acid and Aminocaproic acid which are used to control bleeding due to overdose of fibrinolytics as streptokinase and alteplase (see later).

Adverse effects: intravascular thrombosis.

4- Thromboplastin IM.

5- Antihemophilic globulin (AHG) IV in treatment of hemophilia.

6- Vitamin C in treatment of scurvy.

7- Fresh blood transfusion.

8- Fresh frozen plasma.

9- Aprotinin: blocks plasmin, used for prophylaxis in cardiopulmonary bypass surgery.

❖ ® Sclerosing agents: as sodium morhuate-sylnasol-sodium ricinoleate, used to induce coagulation, and permanent obliteration of varicose veins.



II-Antiplatelet Drugs

(Antithrombotic Drugs = Platelet Aggregation Inhibitors)

Factors stimulating aggregation	Factors inhibiting aggregation
1-Thromboxane A ₂ (TXA ₂). 2-ADP. 3-Glycoproteins (act on specific GPIIb/IIIa receptors on platelets and stimulate binding of fibrinogen to platelets). 4-Ca ²⁺ . 5-Serotonin (5-HT). 6-Collagen	1- Prostacyclin (PGI ₂ ?). 2- c-AMP. 3- c-GMP.

Mechanism of action of Antithrombotics:

A-Inhibition of TXA₂ synthesis

by inhibition of TXA₂ synthetase (platelet COX):

Aspirin (acetyl salicylic acid):

infantile (pediatric) doses of aspirin (75- 150 mg. / day) cause irreversible inhibition of TXA₂ by acetylation of the enzyme. Other NSAIDs are reversible inhibitors and have short duration. Adverse effects: increases incidence of hemorrhagic strokes-bleeding (as from GIT)-allergy.

1- Dazoxiben:

usually combined with aspirin.



B-Inhibition of ADP-dependent pathway:

*these drugs inhibit binding of ADP to ADP receptors on platelets and so inhibit activation of GP IIb/IIIa receptors and inhibit binding of platelets to fibrinogen and to each other. Examples include: Ticlopidine and Clopidogrel (ticlopidine analogue). They are used during stent insertion (* maximum effect after 3-5 days). Adverse effects: bleeding (no specific antidote).*

Ticlopidine may cause neutropenia' but clopidogrel is safer.

C-Blockers of GP IIb/IIIa receptors:

these drugs inhibit binding of fibrinogen to GP IIb/IIIa receptors on platelets and thus inhibit platelet aggregation. They include: Abciximab (monoclonal antibodies of GP IIb/IIIa receptors) - Tirofiban - Eptifibatide.

They are given by IV infusion during surgery and catheterization (oral drugs are too toxic).

Adverse effects: bleeding especially if given with anticoagulants.

D-Prostacyclin analogue: *Epoprostenol (short acting, given IV).*

E-Drugs increasing platelet c-AMP:

Dipyridamole -Cilostazole -Pentoxifylline: inhibit phosphodiesterase leading to increased platelet c-AMP.

** Dipyridamole is ineffective alone and is used in combination with aspirin. It also a vasodilator (* coronary vasodilators) and myocardial stimulant both directly due to increased cardiac c-AMP and reflexly following vasodilatation and hypotension.*

Cilostazole and pentoxifylline are used mainly in treatment of

intermittent claudication.

Indications of Antithrombotics:

Prophylaxis against thrombo-embolism (especially arterial) in old age, stable and unstable angina, after myocardial infarction and cerebrovascular thrombosis.

Common adverse effect:

bleeding, no specific antidote, blood transfusion may be required.



III- Fibrinolytics

Anticoagulants and antithrombotics (antiplatelets)

are used for prophylaxis of thrombo-embolism but they have no effect on already formed thrombi and emboli.

Fibrinolytics dissolve (lyse) already formed thrombi and emboli.

Mechanism of action:

Stimulate conversion of inactive plasminogen (pro-fibrinolysin) into active plasmin (fibrinolysin) which dissolves (lyses) already formed thrombi and emboli.

Indications:

Recently formed thrombi and emboli as in coronary thrombosis causing acute myocardial infarction, cerebro-vascular thrombosis, pulmonary embolism, some cases of deep venous thrombosis (DVT).

They should be given as early as possible before irreversible tissue damage (better results within 3-6 hours).

Examines of Fibrinolytics:

1- Streptokinase:

- *Synthesized by streptococci and is highly antigenic.*
- *Stimulates systemic plasminogen (non selective) causing high incidence of bleeding.*
- *It is given by IV drip (for 1 hour and used within 4 hours, not effective in older thrombi).*
- *Streptokinase does not directly stimulate conversion of plasminogen into plasmin, it stimulates "proactivator" into "activator which stimulates plasminogen conversion into plasmin.*

2- Urokinase:

a human enzyme synthesized by the kidney. It is much less antigenic than streptokinase.

3- Recombinant tissue Plasminogen Activator (r-tPA=Alteplase):

- It is a protease enzyme synthesized by recombinant DNA technology so it is much less antigenic but expensive.
- It binds specifically to local plasminogen bound to fibrin of thrombus or embolus (clot-selective) so it has the advantage of minimal systemic bleeding.
- Shorter 11/2 than streptokinase but more effective in older clots.

4- Other plasminogen activators: Anistreplase- Tenecteplase- Reteplase.

Adverse effects:

1- Bleeding:

more common with streptokinase, and is treated by anti fibrinolytics as tranexamic acid and aminocaproic acid.

Cerebral and GIT bleeding may occur.

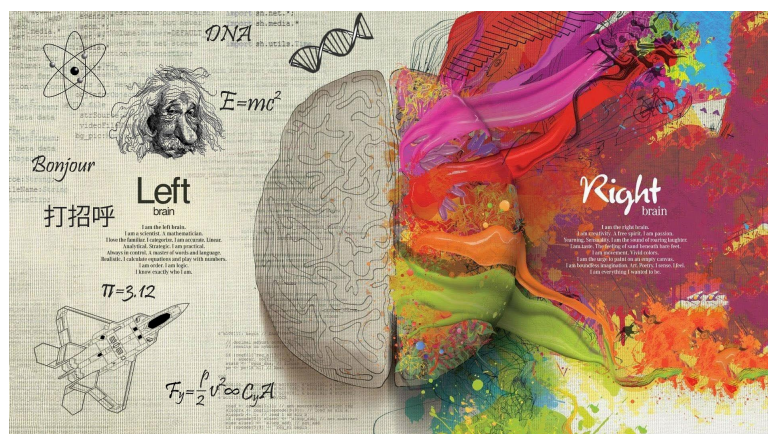
2- Allergic reactions and fever: commonly with streptokinase.

3- Antibodies

to streptococci (due to repeated infections) may inhibit the action of streptokinase.

4-Microemboli.

5-Re-perfusion arrhythmias.



IV- Anticoagulants

Anticoagulants are classified into the following groups:

A-Anticoagulants used in vitro only:

They decrease ionized Ca^{2+} in blood either by precipitation as Na^+ and K^+ oxalate or By de-ionization as Na^+ and K^+ citrate, and EDTA. They are used in blood samples and blood banks during transfusion.

B-Anticoagulants in vivo only (= Indirect acting):

They include oral anticoagulants which interfere with vitamin K activation in the liver: coumarin derivatives: warfarin, dicoumarol, and tromexan.

C- Anticoagulants both in vivo and in vitro (Direct acting):

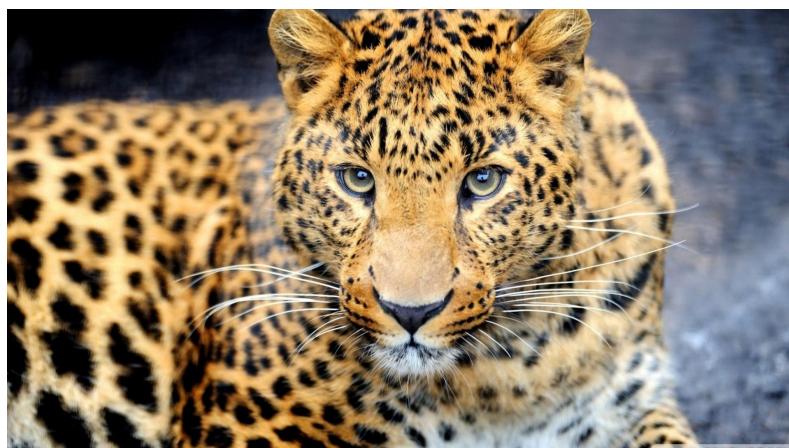
1-Direct thrombin inhibitors (DTIs): hirudin and lipirudin.

2-In direct thrombin inhibitors: act via activation of antithrombin III and include heparins: unfractionated heparin (UFH) and low molecular weight heparin (LMWH).

***Anticoagulants are classified clinically into:**

1- Parenteral anticoagulants: heparin- hirudin - lipirudin.

2- Oral anticoagulants: warfarin.



HEPARINS

I-Unfractionated Heparin (UFH):

Also known as "High Molecular Weight Heparin" (HMWIT).

***Source:**

Animal origin: heparin is naturally present in mast cells with histamine and it is prepared from bovine lung and porcine intestine.

*** Chemistry:**

Mucopolysaccharide - strongly acidic (it is the strongest organic acid) - electro-negatively charged (acidity and negative charge are essential for the anticoagulant activity of heparin).

***Pharmacokinetics:**

•**Absorption:** *heparin is not absorbed orally.*

•**Route of administration:** *heparin is given IV (bolus and infusion) and SC but never IM to avoid hematoma.*

•**Distribution:** *cannot pass placental barrier and is safe during pregnancy.*

•**Fate:** *heparin is rapidly cleared by reticulo-endothelial system (RES), metabolized by the liver and partly excreted unchanged in urine. It is not excreted in breast milk and so it is not contraindicated in lactation.*

***Pharmacodynamics:**

-Mechanism action

Heparin activates "antithrombin III" known as heparin cofactor which in turn inhibits thrombin and other coagulation factors as factor Xa.

Heparin is an indirect thrombin inhibitor.

-Pharmacological actions:

1- Direct anticoagulant characterized by the following:

Advantages:

- Rapid onset: 1-acts directly on coagulation factors in blood
- 2- given IV or SC.
- Acts both in vivo and in vitro.
 - Not contraindicated in pregnancy or lactation.
 - Not liable to drug interactions.

Disadvantages:

* Short duration: due to rapid clearance by RES.

1- Given only by injection and requires careful monitoring of the dose (see later) and accordingly the patient must be hospitalized.

2- Lipemic clearing effect: reduces plasma turbidity after fatty meals due to liberation of lipoprotein lipase.

3- Antiplatelet action (inhibits platelet aggregation) in large doses.



Control of Dose:

1 - Activated Partial Thromboplastin Time (aPTT):

- Normal: about 30-40 seconds.
- After heparin: should be 2-2.5 times the normal value.

2 - Clotting Time (Coagulation time):

- Normal: 5-7 minutes.
- After heparin: should be 2-2.5 times the normal value.

Adverse effects:

1- Hemorrhage is the most serious adverse reaction and it may occur from any site as epistaxis, hematuria, etc. Treated by: stopping heparin + specific antidote (protamine sulphate) + fresh blood transfusion.

2- Hypersensitivity reactions.

3- Thrombocytopenia: which may be mild transient reversible, or severe due to heparin-induced platelet aggregation or heparin-induced antiplatelet antibodies. This may lead to "**paradoxical embolism**". Heparin should be stopped and direct thrombin inhibitors as hirudin and lepirudin are used.

4- Thrombosis: chronic use of heparin reduces antithrombin III activity leading to increased risk of thrombosis.

5- Transient reversible alopecia.

6- Transient reversible osteoporosis (may cause spontaneous fractures).

7- Hyperkalemia: due to inhibition of aldosterone release.

Reversal of action:

- 1- Stop heparin.
- 2- Protamine sulphate is the "specific antidote" of heparin:
-It is strongly basic and electro-positively charged (acts by "chemical antagonism"), 1 mg. protamine IV reverses the action of 100 I.U. heparin.
- 3- Fresh blood transfusion.

Contraindications:

- 1- Hypersensitivity.
- 2- Severe uncontrolled hypertension.
- 3- GIT ulcerations: peptic ulcer and ulcerative colitis.
- 4- Threatened abortion.
- 5- Subacute bacterial endocarditis.
- 6- During and after eye, brain, or spinal cord surgery, or lumbar puncture.
- 7- Bleeding disorders as hemophilia, thrombocytopenia, and purpura.
- 8- Active T.B.
- 9- Intracranial hemorrhage, head injury, and brain tumors.
- 10- Visceral carcinoma.
- 11- Advanced liver and kidney diseases.

II- Low Molecular Weight Heparin (LMWH):

**Examples: Enoxaparin – Daltaparin - Tinzaparin.*

They are obtained by enzymatic depolymerization of UFH.

Advantages over UFH:

- 1- High bioavailability after SC injection and long duration allowing single daily injection.
- 2- Potentiate the action of antithrombin III mainly on activated factor X

(X_a) and have less effect on other coagulation factors; so they are less liable to induce hemorrhage.

3- Equal efficacy as UFH.

4- Predictable pharmacokinetics, so the doses are easily calculated and no need for monitoring by aPTT, and can be used as out-patient therapy.

Heparin-like anticoagulants (Direct Thrombin Inhibitors DTIs):

1- Hirudin: obtained from medicinal leech. Given by IV infusion.

2- Lipirudin: chemically related to hirudin but it is synthesized by recombinant DNA technology. Given IV.

DTIs are indicated in patients with heparin-induced thrombocytopenia, and the main adverse effect is bleeding especially if used with fibrinolytics as streptokinase and alteplase.



**Fondaparinux:*

selective factor X_a inhibitor-given SC once / day-more effective than LMWH in prophylaxis of venous thrombo-embolism as DVT-long $t_{1/2}$ -no need to use antidote (anticoagulation reversal) before stopping (before neurosurgery or if spinal cord injury is suspected).

ORAL ANTICOAGULANTS

Warfarin

****Source:** Synthetic.*

****Chemistry:**■ Coumarin derivative.*

** **Pharmacokinetics:***

*•**Absorption:** absorbed orally.*

*•**Distribution:***

highly bound to plasma proteins (99%)- passes placental barrier and may cause teratogenicity.

*•**Fate:** metabolized by FIME and very small amounts are excreted in breast milk (© not secreted in breast milk).*

****Pharmacodynamics:***

*-**Mechanism of action:** inhibit vitamin K epoxide reductase thus inhibiting regeneration of active reduced vitamin K - from vitamin K epoxide- needed for carboxylation of prothrombin (factor II), factors VII, IX, and X.*

*-**Pharmacological actions:***

Indirect anticoagulant acting in vivo only, characterized by the following:

Advantages.:

- 1- *Easy route of administration.*
- 2- *Long duration of action (4-7 days).*

Disadvantages:

- 1- *Delayed onset (1-2 days): it does not act on already formed active (carboxylated) coagulation factors present in blood but act by inhibiting release of "new" active factors, so the action is delayed until disappearance of the already formed coagulation factors which may take several days.*
- 2- *Liable to several drug interactions (see later).*
- 3- *Contraindicated in pregnancy.*

***Control dose:**

- 1- *Prothrombin time (PT):*
 - Normal: 12-15 seconds.*
 - After oral anticoagulants: PT should be 2-2.5 times the normal value.*
- 2- *International Normalized Ratio (INR): it is a ratio between PT of the patient / PT of control. It should be 2-3 after oral anticoagulation.*



Adverse effects:

- 1- Hemorrhage from any site is the most serious Adverse effect.
- 2- Gut upsets: anorexia, nausea, vomiting, and diarrhea.
- 3- Allergic reactions: skin rash.
- 4- Teratogenicity (abnormal bone development).
- 5- Skin necrosis is rare but serious (may be due to rapid elimination of anticoagulant proteins C and S before coagulation factors are eliminated leading to inability of formation of thrombi in skin blood vessels, it is prevented by co-administration of heparin).
- 6- Drug interactions (see later).

Reversal of action:

- 1- Stop the drug.
- 2- Vitamin K is the specific antidote, e.g. vitamin K1 IV.
- 3- Fresh blood transfusion.

Contraindications:

As heparin + Pregnancy.

Drug interactions:

A-Pharmacokinetic interactions:

•Absorption: cholestyramine decreases absorption of oral anticoagulants. •Distribution: several drugs displace oral anticoagulants from plasma proteins as NSAIDs (aspirin, phenylbutazone, indomethacin), sulphonamides, sulphonylureas, propranolol, verapamil, loop diuretics as frusemide, and clofibrate.

Metabolism:

-HME inducers as phenobarbitone, phenytoin, rifampicin, and tobacco smoking increase clearance of oral anticoagulants and may lead to decreased PT and the patient is at risk of thrombo-embolism.

-HME inhibitors as cimetidine, erythromycin, ketoconazole, chloramphenicol, and allopurinol decrease clearance of oral anticoagulants and may lead to excessive prolongation of PT and bleeding.

B-Pharmacodynamic interactions:

Drugs that increase the effectiveness of oral anticoagulants:

1- Inhibition of vitamin K synthesis by gut bacterial flora: broad spectrum antibiotics especially incompletely absorbed: ampicillin and tetracyclines.

2- Inhibition of vitamin K absorption by liquid paraffin.

3- Inhibition) of vitamin K activation as aspirin (large and toxic doses), and cephalosporins.

These drugs as well as some pathological conditions as liver diseases, obstructive jaundice, and hyperthyroidism (increase catabolism of coagulation factors) increase PT and subject the patient to bleeding.



• **Drugs that decrease the effectiveness of oral anticoagulants:**

- 1- Excess vitamin K (in green vegetables).
- 2- Estrogen (oral contraceptives) increases synthesis of coagulation factors II, VII, IX, X, and inhibits antithrombin III.

These drugs as well as some pathological conditions as hypothyroidism (decreases turnover of coagulation factors) and hereditary resistance to oral anticoagulants decrease PT and subject the patient to thromboembolism.

Factors increasing PT (Increase activity of warfarin)	Factors decreasing PT (Decrease activity of warfarin)
1-Drugs that displace warfarin from plasma proteins. 2-HME inhibitors. 3-Liquid paraffin. 4-Broad spectrum antibiotics. 5-Aspirin (large and toxic doses) and cephalosporins. 6-Pathological conditions as liver diseases, obstructive jaundice, and hyperthyroidism.	1 -Drugs that decrease oral absorption of warfarin as cholestyramine. 2-HME inducers. 3-Excess vitamin K. 4-Estrogen. 5-Pathological conditions as hypothyroidism and hereditary resistance.

Uses of Anticoagulants:

- 1- Anticoagulants are now used primarily in prophylaxis of DVT and pulmonary embolism in high risk patients (smokers-obese-recumbent as postoperative patients-hyperlipidemia and atherosclerosis).
- 2- Unstable angina.
- 3 - Treatment of pulmonary embolism.
- 4- Treatment of acute myocardial infarction.
- 5- Treatment of cerebral thrombosis

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6- *Heparin is used in:*

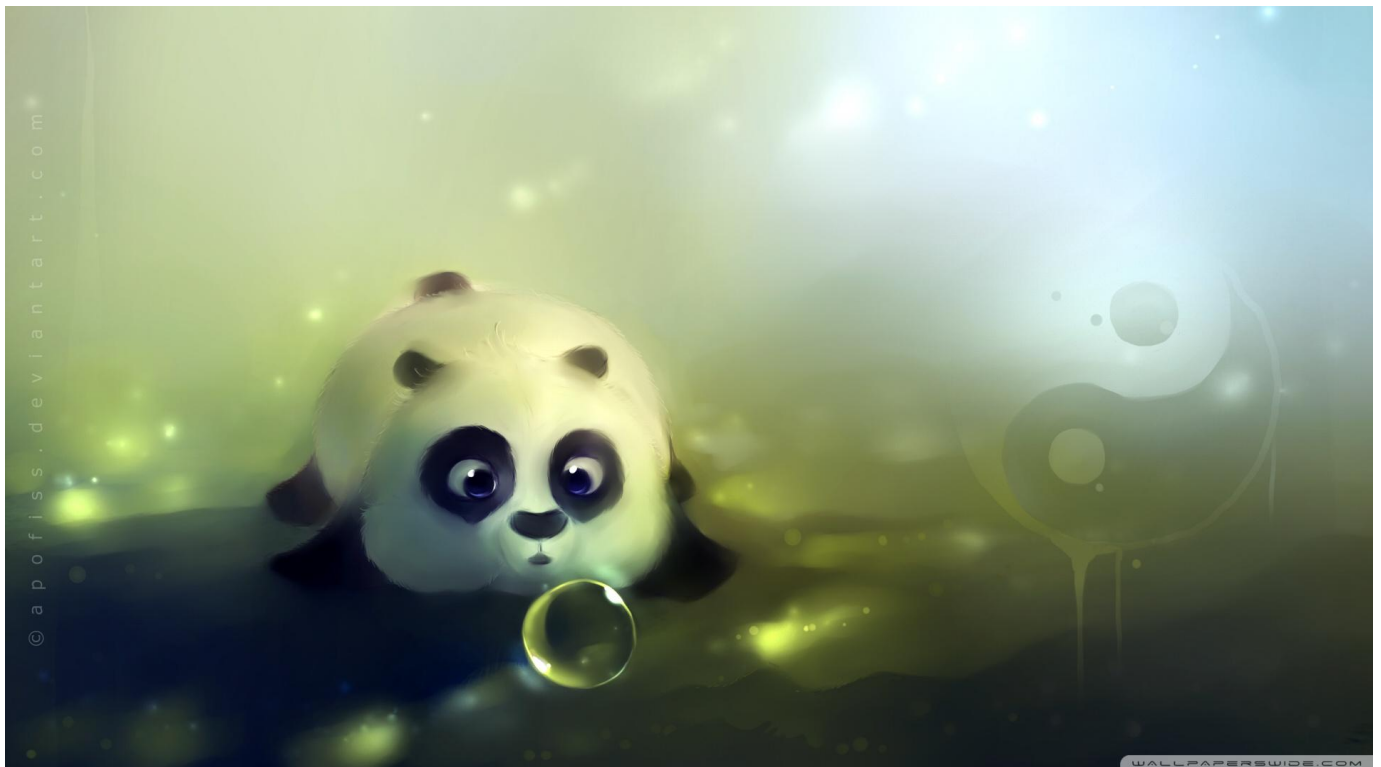
- Disseminated intravascular coagulation (DIC).
- Prevention of blood clotting during blood transfusion and dialysis.
- Hyperlipidemia.

Choice of Anticoagulants:

Start by co-administration of heparin and warfarin for about 4-5 days then heparin is stopped and warfarin, is continued alone after being sure of its anticoagulant action (PT should be 2-2.5 times its normal value).

Remember that during pregnancy heparin is used alone.

Endogenous anticoagulants: 1-Proteins C and S. 2-Antithrombin III.
3-Fibrinolysin.



	HEPARIN	WARFARIN
Source:	<i>Animal origin.</i>	<i>Synthetic.</i>
Chemistry:	<i>Mucopolysaccharide-Strongly acidic-Electronegative.</i>	<i>Coumarin derivative.</i>
Pharmacokinetics:	<i>-Not absorbed orally-given only IV or SC but never IM.</i> <i>-Does not pass placental barrier and not excreted in breast milk. -Rapidly cleared by RES and metabolized by the liver.</i>	<i>Absorbed orally-highly bound to plasma proteins-pass placental barrier-metabolized by the liver and minimally excreted in breast milk.</i>
Pharmacodynamics: -Mechanism:	<i>-Activates antithrombin III and inhibits active factor X, thrombin and other factors.</i>	<i>Inhibits vitamin K epoxide reductase thus inhibiting carboxylation of prothrombin and factors VII, IX, and X.</i>
Actions:	<i>1-Anticoagulant both in vivo and in vitro-Direct-Rapid onset and short duration.</i> <i>2-Lipemia clearing factor.</i> <i>3-Slight V.D.</i> <i>4-Inhibits platelet aggregation.</i>	<i>Anticoagulant in vivo only-Indirect-Slow onset and long duration,</i>
Control of dose:	<i>1-aPTT.</i> <i>2-Coagulation time.</i>	<i>1-PT.</i> <i>2-INR.</i>
Adverse effects:	<i>1-Hemorrhage.</i> <i>2-Hypersensitivity.</i> <i>3-Osteoporosis.</i> <i>4-Alopecia.</i> <i>5-Thrombocytopenia and paradoxical thrombosis.</i> <i>6-Hyperkalemia.</i>	<i>1-Hemorrhage.</i> <i>2-Hypersensitivity.</i> <i>3-Gut upsets.</i> <i>4-Teratogenic and affects suckling babies.</i> <i>5-Skin necrosis.</i>
Reversal of action:	<i>1-Stop the drug.</i> <i>2-Protamine sulphate IV (specific antidote).</i> <i>3-Fresh blood transfusion.</i>	<i>1-Stop the drug.</i> <i>2-Vitamin K IV (specific antidote).</i> <i>3-Fresh blood transfusion.</i>

V-Treatment of Anemias

Treatment of Deficiency Anemias

1 -Treatment of Iron Deficiency Anemia:

- ◆ *Dietary iron is better absorbed from the duodenum in the form of ferrous iron.*
- ◆ *Absorption is enhanced by gastric HCl and vitamin C and reduced by phytate and phosphate.*
- ◆ *Iron deficiency anemia occurs due to dietary deficiency, decreased absorption, and chronic blood loss.*

A-Oral iron preparations:

** Examples:*

Ferrous gluconate, Ferrous fumarate, and iron choline citrate which is the least irritant (Ferrous sulphate is not used as it is very irritant on GIT).

**** Adverse effects:***

- 1- Gut upset: epigastric pain, colics, diarrhea or constipation*
- 2- Acute iron toxicity: manifestations include nausea, vomiting, severe colics, hematemesis, and black or bloody diarrhea. It may cause hypotension, collapse, and finally coma.*

**** Treatment of acute iron toxicity:***

- Stomach wash by NaHCO₃.*
- Iron chelating agent as Desferrioxamine given orally or parenterally.*
- Symptomatic treatment as IV fluids.*

B-Parenteral iron preparations:

** Examples:*

- *Iron dextran: IV or IM.*
- *Iron sorbitol citric acid complex: IM only.*

** Toxicity of parenteral iron:*

- Local effects: pain and skin discoloration at the site of injection.*
- Systemic effects: headache-malaise-muscle and joint pain-
bronchospasm-hemolysis-fainting-hypotension-encephalopathy.*

** Treatment of toxicity:*

- Iron chelating agent as Desferrioxamine given parenterally.*
- Symptomatic treatment as IV fluids.*



Treatment of Pernicious Anemia

◆ *Pernicious anemia is commonly due to deficiency of intrinsic factor required for absorption of vitamin B₁₂ (extrinsic factor).*

◆ *Drugs that decrease absorption of B₁₂ and may cause pernicious anemia include: Metformin, Neomycin, and Para-amino salicylic acid.*

◆ *Manifestations of pernicious anemia include: macrocytic anemia + CNS disturbances (peripheral neuritis and subacute combined degeneration of the spinal cord) + GIT manifestations (glossitis, achlorhydria, gastritis and diarrhea).*

◆Treatment:

- 1- *Cyanocobalamin (1mg. IM may be used for life).*
- 2- *Hydroxocobalamin (also used in treatment of cyanide poisonings cyanide chelating agent).*

N.B.:

- 1- *Never treat pernicious anemia by folic acid alone as it will correct blood picture but aggravates CNS and GIT manifestations.*
- 2- *Neomycin, metformin, and PAS reduce oral absorption of B₁₂.*



Treatment of Folic Acid Deficiency Anemia (Megaloblastic Anemia)

Causes:

- Pregnancy: increases requirements for folic acid.
- Decreases GIT absorption.

Drugs:

- 1- Dihydrofolate reductase inhibitors: Trimethoprim Proguanil
Pyrimethamine.
- 2- Antiepileptic drugs with potent HME induction: Phenytoin Carbamazepine
Barbiturates.
- 3- Methotrexate (antimetabolite anticancer drug).

Treatment:

Folinic acid (active tetrahydrofolic acid = leucovorin).



Blood Disorder	Causes	Treatment
Granulocytopenia (Agranulocytosis):	1-Anti-cancer drugs. 1- Anti-fungal drugs as Amphotericin. 2- Anti-viral drugs as Zidovudine. 3- Anti-thyroid drugs: Thioamides as methimazole and-carbimazole. 4- Anti-inflammatory drugs: Pyrazolone derivatives (phenylbutazone), Indole derivatives (indomethacin), gold salts (used in rheumatoid arthritis). 5-Anti-bacterial drugs: chloramphenicol and sulphonamides. 6-Anti-epileptic drugs: carbamazepine.	1-Stop the drug. 2- Fresh blood transfusion. 3- Broad spectrum penicillins. 4- Anabolic steroids and glucocorticoids. 5- Hematopoeitic growth factors as erythropoietin, granulocyte colony stimulating factor (G- CSF), or granulocyte / macrophage colony stimulating factor (GM-CSF).
Aplastic Anemia:	Ionic inhibitors as perchlorate (were used as antithyroid drugs) + most of the drugs causing granulocytopenia.	1-Stop the drug. 2- Fresh blood transfusion. • 3- Anabolic steroids and glucocorticoids. 4- Hematopoeitic growth factors as erythropoietin. 5- B12, folic acid, and vitamin C.
Methemoglobinemia:	1-Primaquine. 2- Sulphonamides. 3- Phenacetin. 4- Nitrites (more than nitrates).	Reducing agents as vitamin C (ascorbic acid) or methylene blue.
HEMOLYTIC ANEMIA (IN DEFICIENCY OF G-6-PD):	1 -Aspirin. 2- Sulphonamides. 3- Primaquine. 4- Phenacetin. 5- Isoniazid.	1- Avoid drugs inducing hemolysis. 2- Fresh blood transfusion or packed RBCs.

VI- Treatment of Hyperlipidemias

	STATINS	FIBRATES	Bile acid sequestrants (bile acid-binding resins)
Examples	Simvastatin- Lovastatin- Pravastatin- Atorvastatin.	Clofibrate- Fenofibrate- Gemfibrozil	Cholestyramine- Colestipol
Actions	1- decrease cholesterol synthesis by inhibition of HMG Co-A reductase. 2- decrease LDL in bloodcompensatory increase in hepatic LDL receptors—» increase uptake of cholesterol by hepatocytes. 3- increase HDL 4- decrease Triglycerides.	1- decrease Triglycerides by decrease VLDL synthesis and output from the liver (by decrease lipolysis in adipose tissues and decrease FFA supply to the liver) and increase VLDL clearance from plasma (increase activity of lipoprotein lipase). 2- decrease LDL. 3-increase HDL (most effective, especially gemfibrozil).	1- Bind to (sequester) bile salts in the intestine inhibiting their entero-hepatic recyclecompensatory increase in hepatic LDL receptors ...increase uptake of cholesterol by hepatocytes to synthesize bile salts. 2- Decrease LDL. 3-No effect on HDL or triglycerides.
Uses	All types of hyperlipidemias (the most effective drugs).	Hypertriglyceridemia- Mixed hyperlipidemia.	Hypercholesterolemia in patients intolerant to other drugs.
Adverse effects	1 -increase liver enzymes (transaminases) and may be hepatotoxic.	1-increase liver enzymes and may be hepatotoxic. 2- increase creatine kinase (CK) and may	1- Constipation and distension (may be used in treatment of refractory diarrhea, see GIT pharmacology).

	2- increase creatine kinase (CK) and may cause myopathy. 3- Gut upset. 4- Headache. 5- Teratogenic. 6-Displace oral anticoagulants from plasma proteins.	cause myopathy. 3- Gut upset. 4- Gall stones (cholelithiasis) and cholecystitis. 5- Displace oral anticoagulants and sulphonylureas from plasma proteins. 6-Allergy and blood dyscrasias.	2-Decrease absorption of most drugs as digitalis, warfarin, and fat-soluble vitamins
Contra-indications	1-Pregnancy and lactation. 2-Liver diseases.	1-Pregnancy-lactation. 2-Liver diseases. 3-Gall bladder diseases	



Other Antihyperlipidemic Drugs

Niacin (nicotinic acid): as fibrates (decrease LDL and VLDL synthesis by the . liver and increase lipoprotein lipase —>decrease cholesterol and triglycerides).

Adverse effects:

- 1- *flushing due to PG release, this is prevented by aspirin administration before niacin.*
- 2- *GIT disturbances.*
- 3- *Hyperuricemia and hyperglycemia.*
- 4- *Elevation of serum transaminases.*

Ezetimibe: decreases absorption of dietary and biliary cholesterol.

